Remarks

I. Status of the Application and Claims

As originally filed, the present application had a total of 23 claims. As the result of a restriction requirement, all claims except for 12-16 were cancelled and new claims 24-30 were added in a response filed by Applicants on May 13, 2003. All of the presently pending claims have received a final rejection in an Office Action dated August 4, 2003.

II. The Amendments

Claim 24 has been amended to change it from a method of "preventing the formation of atherosclerotic lesions" to a "method of treating atherosclerotic lesions." Support for the amendment may be found on page 2 of the application, lines 15-20. In addition, a minor amendment was made to claim 13 to correct a grammatical error. These amendments do not add new matter to the application and their entry is respectfully requested.

The Rejections

I. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

On pages 4 and 5 of the Office Action, the Examiner rejects claims 24-29 under 35 U.S.C. § 112, first paragraph, based upon the allegation that the specification provides enablement for the treatment of a patient with atherosclerosis, but does not provide enablement for preventing the formation of an atherosclerotic lesion. Although Applicants do not fully agree with the Examiner on this point, in the interest of furthering the prosecution of this case, claim 24 has been amended so that it now is directed to a method of treatment rather than a method of prevention. Treatment would occur in cases where a drug is administered to a patient presenting evidence of atherosclerotic disease. Naturally, treatment may include an element of prevention in the sense that further disease development is inhibited. Prevention that occurs concurrently with treatment is not excluded by the amended claim. In light of this amendment, Applicants believe that the Examiner's rejection has been overcome, and it is therefore respectfully requested that this rejection be withdrawn.

II. Rejection of Claims Under 35 U.S.C. § 103

The Examiner maintains a rejection of all pending claims under 35 U.S.C. § 103 based upon the allegation that claims would be obvious in light of Shaish, *et al.* (*J. Clin. Invest. 96*:2075-2082 (1995)) in combination with Samokyszyn, *et al.* (*J. Biol. Chem. 262*:14119-14133 (1987)). The Examiner alleges that Shaish teaches that all-trans isomers of beta-carotene inhibit the formation of atherogenic lesions and that metabolites of all-trans forms of beta-carotene inhibit atherosclerosis. Although the reference fails to teach that oxidized forms of retinoic acids or beta-carotene are involved in this process, the Office Action alleges that the Samokyszyn reference discloses that oxidized forms of retinoic acid are pharmacologically active. The Examiner admits that Samokyszyn does not teach the specific oxidized retinoic compounds of the present claims, but nevertheless asserts that, based upon its teachings, it would have been obvious to use retinoic acid (both the cis and trans forms) in the treatments taught by Shaish.

Applicants respectfully traverse this rejection.

The Examiner's argument depends upon the Samokyszyn reference teaching that oxidized forms of retinoic acids represent the forms that are active. However, the reference by Samokyszyn is confined entirely to activity with respect to tumor promotion (see page 1219, col. 1). This activity has no clear relationship to atherosclerosis. To the extent that a mechanism is described in the Samokyszyn reference, it suggests that the ability of retinoids to act as free radical scavengers plays an important part in the effects observed with respect to tumors (see page 1429, col. 1, second full paragraph). In contrast, Shaish clearly indicates that the activity of all-trans beta-carotene on atherosclerosis is unrelated to its ability to act as a free radical scavenger and, instead, probably relates to stereospecific interactions with receptors on arterial walls (see Abstract of Shaish). Thus, Applicants cannot see any motivation for one of skill in the art to combine the teachings of Shaish and Samokyszyn. The references are concerned with entirely distinct biological conditions that do not share any readily apparent etiological mechanism.

Applicants do not dispute the Examiner's assertions that Shaish teaches that metabolites derived from all-trans beta-carotene inhibit atherosclerosis. However, there are a multitude of metabolites that fit this description and there is nothing that would lead one of skill in the art to the particular compounds recited in Applicants' claims. Moreover, the metabolites referred to in Shaish could undergo extensive processing before they reach an active form, thereby enlarging the number of possible compounds responsible for the activity observed. In light of this, Applicants, again, can see no motivation for combining the teachings in Shaish with those in the Samokyszyn paper. In addition, Applicants do not see how the combined teachings would lead to the specific compounds in the present claims.

On page 4 of the Office Action, the Examiner argues that, based upon the teachings of Samokyszyn, one of skill in the art would be motivated to use both cis and trans forms of oxidized retinoic acid in the prevention of atherosclerosis as set forth in Shaish. However, there are express teachings in Shaish indicating that cis and trans forms of oxidized retinoic acid will *not* have similar effects. For example, on page 2080, col. 1, second paragraph, Shaish says: "It is of interest that *all-trans* beta-carotene but not 9-cis beta-carotene reduced lesion formation in hypercholesterolemic rabbits." This clearly demonstrates that the teachings of Samokyszyn with respect to the effects of metabolites on tumors cannot be applied with any degree of confidence to the teachings of Shaish with respect to atherosclerosis. They are two distinct biological conditions.

Finally, the Examiner implies on page 6 of the Office Action that even if Samokyszyn does not suggest that compounds can be used to treat atherosclerosis, this is irrelevant because the suggestion regarding atherosclerosis is found in the Shaish reference itself. This argument fails to consider whether a motivation exists for combining the references. There is no suggestion in either reference that there is a relationship between cancer and atherosclerosis that would provide a basis for believing that the metabolites active for one of these conditions should also be active in the other. In fact, using the example regarding 9-cis

beta-carotene discussed above, there seems to be very good reasons for concluding that one cannot reasonably extrapolate the results obtained from one disease to the other.

In light of these considerations, Applicants submit that: a) a valid motivation for combining references has not been established; b) that the references cited fail to provide any guidance as to which of a large number of possible metabolites might be involved in atherosclerosis; and c) that, even if references are combined, one would not arrive at the compounds of the present claims. Applicants therefore submit that the rejection of claims under 35 U.S.C. § 103 has been overcome and respectfully request that this rejection be withdrawn.

Conclusion

In light of the amendments and discussion above, Applicants submit that all of the Examiner's rejections have been overcome. It is therefore respectfully requested that these rejections be withdrawn and that the claims presently pending in the application be allowed.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (202) 419-7013.

Respectfully submitted,

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